

# CLINICAL TREATMENT GUIDELINE FOR THE MANAGEMENT OF HYPERTHYROIDISM IN ADULTS 2024



**Ministry of Health  
Republic of Maldives**



**World Health Organization  
Maldives**

**RELEASE RECORD**

Version Number	Version Date	Description of change
1	2024	Initial release

**DOCUMENT NUMBER: MOH/QA/G/24/182-0**

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<b>Published by:</b>	Ministry of Health in collaboration with WHO Maldives

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## 1.0 INTRODUCTION

Hyperthyroidism is a common thyroid disorder characterized by increased synthesis and secretion of thyroid hormones from the thyroid gland, or from an endogenous or exogenous extra thyroidal source. The most common causes of hyperthyroidism include Graves' disease, toxic multi nodular goiter and toxic adenoma. Hyperthyroidism can be overt or subclinical. Overt hyperthyroidism is characterized by elevated serum free T4 or T3 concentrations with a suppressed TSH level. Subclinical hyperthyroidism is a milder form which is defined as low or suppressed TSH with normal free T4 and T3 within the reference interval.<sup>6,7</sup>

Thyrotoxicosis is the clinical state associated with excess thyroid hormone activity in tissues, due to the increased level of elevated circulating thyroid hormones in the body. The clinical presentation of hyperthyroidism varies, ranging from asymptomatic to life-threatening thyroid storm. Thyroid hormones affect almost every organ system in the body and are associated with increased tissue thermogenesis and basal metabolic rate. The typical symptoms of weight loss, heat intolerance and palpitations are due to the hyper metabolic state induced by excess thyroid hormones. Some of the most profound effects of increased thyroid hormone levels are on the cardiovascular system. Untreated, hyperthyroidism can result in marked loss of weight, osteoporosis, atrial fibrillation, embolic events, and even cause cardiovascular collapse and death.<sup>9</sup>

Hyperthyroidism can be treated with either antithyroid drugs, radioactive iodine therapy or surgical thyroidectomy, where the choice of treatment option, depends on the underlying etiology, the presence of contraindications to a particular treatment modality, the severity of hyperthyroidism and the patient's preference.<sup>6</sup>

## 2.0 SCOPE OF THE GUIDELINE

Although hyperthyroidism is a common endocrinological condition seen among the patients presenting to healthcare facilities, in the Maldives, no local guideline has yet been developed for the management of the condition and hence represents a priority area, in need of updated, evidence-based practice guidelines.

This guideline has been developed in this regard as a guidance document for health care professionals and is based on currently published evidence-based practices for screening, diagnosis and management of hyperthyroidism. It is intended to assist health care professionals to deliver rational, current and optimum medical care to treat hyperthyroidism in adults.

The target audience for this guideline includes general and specialist medical practitioners and other health care workers providing care for patients with hyperthyroidism.

It is also intended as a reference document to be used by health care policy makers as an assistance in formulating health care policy decisions regarding the management of thyroid disease.

### 3.0 CAUSES OF HYPERTHYROIDISM

<b>Graves' disease</b>	The most common cause of hyperthyroidism. It is an autoimmune disorder characterized by the presence of anti-TSH receptor antibodies (TRAb), resulting in an overactive thyroid gland, ocular abnormalities (Graves' orbitopathy) and localized dermopathy which is rare (pretibial myxedema). <sup>4</sup> It is associated with the occurrence of other autoimmune disorders such as type I diabetes mellitus, celiac disease and vitiligo.
<b>Toxic adenoma or multinodular goiter</b>	Autonomous nodules that produce thyroid hormone without TSH stimulation.
<b>Thyroiditis</b>	Destruction of the thyroid follicle cells resulting in release of preformed thyroid hormones. It could be due to autoimmune processes such as Hashimoto's thyroiditis, infective like sub-acute thyroiditis or anaplastic carcinoma of the thyroid gland or primary thyroid lymphoma
<b>Drug induced thyroiditis</b>	Over production or release of preformed thyroid hormones can occur with amiodarone, interferon alpha, interleukin-2 or lithium. <sup>6</sup>
<b>Gestational hyperthyroidism</b>	Develops in the first trimester of pregnancy because of the stimulatory action of placental human chorionic gonadotropin, which shares structural features with TSH, on the thyroid gland <sup>6</sup>
<b>Hyperemesis gravidarum</b>	High level of stimulates human chorionic gonadotropin TSH receptors
<b>Post-partum thyroiditis</b>	Variant of painless thyroiditis occurring within 12 months postpartum
<b>Endogenous sources of thyroid hormones</b>	Include struma ovarii, where ectopic thyroid tissue in ovarian dermoid tumour produces thyroid hormones and metastatic thyroid carcinoma secreting thyroid hormones, both of which are rare. <sup>6</sup>
<b>TSHoma</b>	Pituitary adenoma secreting excessive amounts of TSH leading to secondary hyperthyroidism
<b>Factitious thyrotoxicosis</b>	Surreptitious ingestion of thyroid hormones

## 4.0 CLINICAL MANIFESTATIONS

- The clinical presentation of hyperthyroidism can range from asymptomatic to thyroid storm. The classic symptoms of hyperthyroidism include heat intolerance, tremor, palpitations, anxiety, retraction of eyelids and increased frequency of bowel movements. The elevated thyroid hormone levels increase the body's metabolism which induces weight loss despite a normal or increased appetite and causes a variety of symptoms in many systems<sup>6</sup>(Table 1 and 2).  
Patients with long standing untreated hyperthyroidism may develop atrial fibrillation, heart failure and osteoporosis. <sup>6</sup>

**Table 1: Symptoms of Hyperthyroidism**

- Nervousness
- Irritability and Anxiety
- Increased perspiration
- Heat intolerance
- Tremors
- Hyperactivity
- Palpitations
- Insomnia
- Hyper defecation
- Weight loss despite increased appetite
- Proximal muscle weakness
- Blurred vision, diplopia, grittiness sensation in eyes
- Irregular menstruation

**Table 2: Signs of Hyperthyroidism**

- Tachycardia, irregular pulse
- Warm, moist, smooth skin
- Staring look, retraction of eye lids and Lid lag
- Peri orbital edema and Exophthalmos
- Hand and tongue tremors
- Brisk peripheral reflexes with accelerated relaxation phase
- Proximal muscle weakness
- Goiter with or without bruit

## 5.0 DIAGNOSIS

The diagnosis of hyperthyroidism is based on clinical suspicion from the patient's symptoms and signs at presentation, which is then confirmed by laboratory testing.

### 5.1 Examination of the patient

5.1.1 All patients with symptoms suggestive of hyperthyroidism should undergo a comprehensive physical examination for signs of hyperthyroidism (Table 3). If there is clinical suspicion of hyperthyroidism, it should prompt laboratory testing of thyroid function tests to establish the diagnosis.

**Table 3: Examination of patients with symptoms suggestive of hyperthyroidism**

<ul style="list-style-type: none"> <li>• Measurement of pulse rate blood pressure, respiratory rate, temperature</li> <li>• Measuring Body Weight</li> <li>• Examination of the thyroid gland for size, presence or absence of thyroid tenderness, symmetry and nodularity</li> <li>• Presence or absence of tremors</li> <li>• Peripheral edema</li> <li>• Eye signs- lid lag, lid retraction, exophthalmos</li> <li>• presence of pretibial myxedema</li> <li>• Examination of pulmonary, cardiac, and neuromuscular function</li> </ul>
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### 5.2 Investigations for Diagnosis of Hyperthyroidism

#### 5.2.1 Laboratory investigations

5.2.1.1 In all patients with suspected hyperthyroidism, Serum TSH level should be used as the initial screening test as it has the highest sensitivity for diagnosis hyperthyroidism.<sup>7,9</sup>

If TSH level is suppressed, then "Reflex testing" of free T4 from the same blood sample should be triggered by the laboratory

5.2.1.2 If hyperthyroidism is strongly suspected, it is recommended to do a free T4 along with TSH as the initial investigation.

5.2.1.3 Free T3 should be measured in cases where TSH is suppressed with normal FT4

- In overt hyperthyroidism, TSH is suppressed with increased free T4 and/or increased free T3 levels. In T3 thyrotoxicosis TSH is suppressed with normal free T4 and increased free T3.

Subclinical hyperthyroidism is defined by a low TSH(<0.4mU/L), in the presence of normal free T4 and free T3.<sup>7</sup>

5.2.1.4 TSH receptor antibody (TRAb) testing is recommended to establish the cause of hyperthyroidism.

- TSH receptor antibodies (TRAb) are specific biomarkers for the diagnosis of Graves' disease. They are also useful for predicting the risk of relapses and guide definitive treatment for Graves' disease. <sup>11</sup>

### 5.2.2 Imaging

5.2.1.5 Thyroid Ultrasound is recommended in the presence of palpable thyroid nodule or goiter to characterize the thyroid nodules and goiter.

5.2.1.6 Thyroid ultrasound with doppler examination is recommended to detect enlargement of the thyroid gland and to detect increased vascularity in Graves' disease, if the clinical presentation and initial biochemical evaluation is not sufficient for the diagnosis.<sup>11</sup>

5.2.1.7 Scintigraphy of the thyroid gland is indicated in specific cases and should be only recommended by an endocrinologist.

## 6.0 MANAGEMENT OF HYPERTHYROIDISM

- Once the diagnosis of hyperthyroidism is established, prompt treatment is required because of the deleterious effects of excess thyroid hormone on multiple organ systems. Referral to a specialist evaluation by a physician or endocrinologist when available should be done to determine appropriate diagnosis and treatment in primary health care settings.
- In all women of childbearing age who are thyrotoxic the possibility of future pregnancy should be discussed. Counseling should take into consideration the woman's desired timeline to conception and include a discussion of the risks and benefits of all treatment options.
- Regardless of the cause of hyperthyroidism, adrenergic symptoms in hyperthyroid patients are to be treated with short term beta blockers. <sup>11</sup>

### 6.1 Treatment for adrenergic symptoms

6.1.1 Beta blockers should be given to all symptomatic patients with hyperthyroidism.

- Treatment with Beta-blockers leads to a decrease in heart rate, systolic blood pressure, muscle weakness, and tremor and an improvement in the degree of irritability and exercise intolerance.  
The patient's underlying comorbidities and clinical situation should be considered when choosing the beta blocker to be used.

- Beta blockers used to treat adrenergic symptoms in hyperthyroidism include:
  - Propranolol 20 to 40 mg orally every 6 to 8 hours. It has the longest experience and widest use in adrenergic symptom management in hyperthyroidism
  - Atenolol 25- 100mg 1-2 times daily
  - Metoprolol 25 to 50 mg 2 times daily
  - Bisoprolol 5-10mg daily
  - IV Esmolol 0.25 to 0.5 mg/kg as initial loading dose followed by continuous infusion of 0.05 to 0.1 mg/kg per minute (should be given in an intensive care setting with monitoring)
- In patients who do not tolerate or are not candidates for use of beta blockers, calcium-channel blockers, both verapamil and diltiazem, can be used. <sup>7,9</sup>

## 6.2 Treatment options for Hyperthyroidism

- The three treatment options in Hyperthyroidism include:
  - Anti -Thyroid Drugs
  - Radioactive Iodine therapy (I-131) ablation of the thyroid gland
  - Surgical thyroidectomy.
- The suitability of the treatment option would depend on the cause of hyperthyroidism and the specific patient circumstances.

6.2.1 In uncomplicated Graves' disease the recommended first line therapy is anti-thyroid drugs.

- Approximately 30 -50% percent of people with Graves' disease will have a remission after one to two years on anti-thyroid drugs.  
The treatment itself might have a beneficial immunosuppressive role, either to primarily decrease thyroid-specific autoimmunity, or secondarily, by ameliorating the hyperthyroid state, which may restore the dysregulated immune system back to normal.  
Antithyroid drugs are easy to take and can be easily modified or discontinued when indicated.

6.2.2 In Graves' disease when remission is not achieved with the anti-thyroid drugs or in cases of relapse, definitive treatment is recommended with either radioactive or total thyroidectomy.

6.2.3 In Graves' disease with the presence of moderate to severe thyroid eye disease the definitive treatment recommended is total thyroidectomy.

- Radioactive iodine therapy has been associated with the development or worsening of thyroid eye disease and should be avoided as a treatment option for hyperthyroidism in patients with active thyroid eye disease.  
The risk of worsening thyroid eye disease is increased in smokers, in patients with pre-existing significant eye symptoms and those with severe hyperthyroidism or high TRAb levels.
  - 6.2.4 In toxic adenoma and multi-nodular goiter, radioactive ablation and thyroidectomy are the main treatment options.
  - 6.2.5 Long-term treatment of toxic nodular goiter with anti- thyroid drugs might be indicated in some elderly or otherwise ill patients with limited life expectancy, who are not good candidates for surgery or ablative therapy or in patients who prefer this option.<sup>6, 11</sup>
- The management decision to decide on the treatment option should include the advantages and disadvantages of each treatment option (Table 4), the clinical situation (Table 5), expected speed of recovery and the patient values and preferences <sup>6,11</sup>

**Table 4: Possible Advantages and Disadvantages of the Treatment Options for Hyperthyroidism**

Option	Advantages	Disadvantages
<b>Anti-thyroid drugs</b>	<ul style="list-style-type: none"> <li>▪ Non-invasive treatment</li> <li>▪ Possibility of remission and preservation of thyroid function</li> <li>▪ Convenient and cost of treatment is low</li> <li>▪ Available in primary care setting</li> </ul>	<ul style="list-style-type: none"> <li>▪ Rare but serious side-effects such as agranulocytosis, hepatic damage, pancreatitis, pruritus, cutaneous reactions</li> <li>▪ Requires frequent monitoring</li> <li>▪ Risk of birth defects in pregnancy</li> </ul>
<b>Radioiodine</b>	<ul style="list-style-type: none"> <li>▪ Noninvasive treatment with an excellent cure rate of hyperthyroidism</li> </ul>	<ul style="list-style-type: none"> <li>▪ Not available in Maldives at present</li> <li>▪ Radiation exposure to salivary glands</li> <li>▪ Permanent hypothyroidism in most cases</li> <li>▪ Need for short-term radiation protection (limited contact with other people for a few days after treatment)</li> <li>▪ Need to avoid becoming pregnant or fathering a child till 6 months)</li> <li>▪ Potential adverse effects on fertility</li> <li>▪ Risk of exacerbation of Graves orbitopathy</li> </ul>
<b>Thyroidectomy</b>	<ul style="list-style-type: none"> <li>▪ Rapid and permanent resolution of hyperthyroidism</li> <li>▪ May improve thyroid eye disease</li> <li>▪ Relief of compressive symptoms in large goiters</li> </ul>	<ul style="list-style-type: none"> <li>▪ Invasive treatment</li> <li>▪ Permanent hypothyroidism</li> <li>▪ Risk of surgery and anesthesia</li> <li>▪ Possible underactive parathyroid and low calcium</li> <li>▪ Possible changes to the voice</li> </ul>

**Table 5: Clinical situations that help to decide on a particular treatment option for hyperthyroidism**

Treatment option	Clinical Situations in favor of	Contraindications
<b>Radioactive Iodine</b>	<ul style="list-style-type: none"> <li>▪ Women not planning a pregnancy in the future (in less than 6 months)</li> <li>▪ Individuals with comorbidities that increase surgical risk</li> <li>▪ Prior surgery or externally irradiated neck</li> <li>▪ Lack of access to a high-volume thyroid surgeon</li> <li>▪ Patients with contraindications to anti-thyroid drugs</li> <li>▪ Elderly or Patients with significant comorbidity</li> </ul>	<ul style="list-style-type: none"> <li>▪ Pregnancy and Lactation</li> <li>▪ Coexisting thyroid cancer, or suspicion of thyroid cancer</li> <li>▪ Individuals unable to comply with radiation safety guidelines</li> <li>▪ Women planning a pregnancy within 4- 6 months</li> </ul>
<b>Anti-thyroid Drugs</b>	<ul style="list-style-type: none"> <li>▪ Patients with a high likelihood of remission. (mild disease, small goiter and negative or low-titre TRAb)</li> <li>▪ Pregnancy</li> <li>▪ Elderly or others with comorbidities that increase surgical risk or with limited life expectancy</li> <li>▪ Patients with previously operated or irradiated necks</li> <li>▪ Patients with lack of access to a high-volume thyroid surgeon</li> <li>▪ Patients with moderate to severe active thyroid eye disease</li> </ul>	<ul style="list-style-type: none"> <li>▪ Previous known major adverse reactions to Anti thyroid drugs</li> </ul>
<b>Surgery</b>	<ul style="list-style-type: none"> <li>▪ Symptomatic compression or large goiters (&gt;80 g)</li> <li>▪ Thyroid malignancy documented or suspected</li> <li>▪ Substernal or retrosternal extension</li> <li>▪ Large thyroid nodules, especially if greater than 4 cm or if nonfunctioning, or hypo functioning</li> <li>▪ Coexisting hyperparathyroidism requiring surgical intervention</li> <li>▪ If TRAb levels are particularly high</li> <li>▪ Patients with moderate to severe active thyroid eye disease</li> </ul>	<ul style="list-style-type: none"> <li>▪ Comorbidities such as severe cardiopulmonary disease, end-stage cancer</li> <li>▪ Lack of high-volume thyroid surgeon</li> <li>▪ Pregnancy, a relative contraindication. (Surgery should only be used when rapid control is required, and anti-thyroid medicines cannot be used)</li> </ul>

### 6.3 Treatment with Anti-thyroid drugs

- Anti-thyroid drugs are the usual preferred initial treatment in hyperthyroidism and are favorable due to the possibility of remission of hyperthyroidism. Patients with mild hyperthyroidism, minimally enlarged thyroid and mildly elevated TRAb levels are particularly good candidates for anti-thyroid drug therapy as they have the best chance of achieving a durable remission. <sup>2</sup>
- The dose of anti-thyroid drugs should be targeted to the degree of thyroid dysfunction. Thus, it is important to use a dose that will achieve the clinical goal of normalization of thyroid function reasonably rapidly while minimizing adverse drug effects.
- The drugs used to treat hyperthyroidism are Carbimazole or its active metabolite methimazole and propylthiouracil. Carbimazole is widely available and used locally for the treatment of hyperthyroidism. It has the advantage of being given as a once daily dosing and with less risk of hepatotoxicity compared to propylthiouracil.<sup>7,9</sup>

6.4.1 Carbimazole is the recommended first line of anti-thyroid medication in all patients who are treated with anti-thyroid drug therapy.

6.4.2 Carbimazole should be given for a duration of 12 to 18 months as initial treatment for Graves' disease in patients with possibility of remission.

6.4.3 At the start of carbimazole therapy, initial doses of 10-40 mg daily are used to restore euthyroid and the dose can then be titrated down to a maintenance level, generally 5 - 10 mg daily. <sup>9</sup>

6.4.4 Women treated with carbimazole should be switched to propylthiouracil when planning pregnancy or during the first trimester of pregnancy.<sup>9</sup>

6.4.5 Propylthiouracil is recommended as first line agent in women planning pregnancy and during the first trimester of pregnancy.

6.4.6 Propylthiouracil is recommended as second line agent in patients who do not tolerate carbimazole or do not respond to carbimazole.

- Propylthiouracil has a shorter duration of action and is usually administered two or three times daily, starting with 50-150 mg three times daily and is titrated depending on the severity of the hyperthyroidism.
- All patients should have a Liver function test and a complete blood cell count done before starting anti-thyroid drugs. <sup>11</sup>

## 6.4 Side effects of Anti- thyroid Drugs

- Adverse reactions include minor allergic reactions including pruritus or a limited minor rash to rare severe side effects such as agranulocytosis, vasculitis and hepatic damage. Agranulocytosis is a rare but serious adverse effect of carbimazole<sup>9</sup>. Anti-thyroid drug associated neutropenia typically develops usually in the first month of treatment but there are rare cases of patients developing neutropenia after many years of treatment.
- All patients should be informed of the potential side effects of anti-thyroid drugs, ideally given written instructions regarding the necessity of consulting the doctor promptly if they should develop jaundice, light-colored stools, dark urine, fever, sore throat or mouth ulcers, while on anti-thyroid drugs.<sup>9,11</sup>

- 6.4.1 Patients and caregivers should be counseled about the side effects of anti-thyroid drugs at the start of treatment.
- 6.4.2 Side effects such as minor cutaneous reactions, are to be managed symptomatically with antihistamines while continuing anti-thyroid drugs.
- 6.4.3 In the presence of mucosal blistering, which may indicate Stevens-Johnson syndrome, the anti-thyroid drugs should be stopped immediately.
- 6.4.4 In case of a serious allergic reaction, switching to alternative drug is not recommended and patients should be advised for definitive treatment with total thyroidectomy or radioactive iodine therapy.<sup>9</sup>
- 6.4.5 Any patient with signs or symptoms of infection, sepsis, including fever or a sore throat, while on treatment, should seek urgent medical care and get a white blood cell count done.<sup>9</sup>
- 6.4.6 If the neutrophil count is below  $0.5 (\times 10^9/L)$ , anti-thyroid drugs should be stopped, and alternative treatment should be initiated with referral to an endocrinologist. A neutrophil count between 0.5 and 1.5 can be monitored closely with once or twice weekly measurements until stable.
- 6.4.7 Liver function tests should be performed in the event of signs of liver dysfunction including jaundice, dark urine or light-colored stools.
- 6.4.8 An increased transaminase level  $> 3$  times the upper limit of normal during treatment, warrants anti-thyroid drug cessation and referral to an endocrinologist. Liver function should be monitored till resolution.
- 6.4.9 Anti-thyroid drugs should not be advised for an individual who has experienced serious side effects or complication linked to earlier administration.

6.4.10 Total thyroidectomy or radioactive iodine therapy are treatment options for patients who develop side effects such as severe neutropenia or significant liver dysfunction with anti-thyroid drugs.

## 6.5 Monitoring patients on anti-thyroid drugs

- Most patients will be biochemically euthyroid within 4-8 weeks, although the timeline will depend on disease severity, anti-thyroid drug dose and compliance. Patients with higher baseline thyroid hormone concentrations may take a longer time to normalize.
- As the patient becomes euthyroid or hypothyroid, the anti-thyroid drug dose, can then be reduced by approximately 25-50% (euthyroid) or 50% (hypothyroid). If the patient remains hyperthyroid, then the dose can be increased by approximately 25%, or more if the hyperthyroidism is severe.

6.5.1 Patients' thyroid status should be assessed by thyroid hormone levels every 4 weeks for the first 3 months, after initiation of therapy and the dose of medication adjusted accordingly.

6.5.2 FT4/T3 should be used to guide titration of treatment.

- Serum TSH may remain suppressed for several months after the initiation of therapy, hence TSH is not a good parameter for monitoring therapy during the initial months.<sup>9,11</sup>

6.5.3 Once euthyroid levels are reached, thyroid function tests can be done at intervals of 3 months.

## 6.6 Stopping anti-thyroid drugs

- Patients are more likely to undergo remission at the end of 12-18 treatment if they have normal TSH, are on a low dose of carbimazole 5mg daily or less, have normal or no detectable TRAb, no large goiter and no active thyroid eye disease.
- Measurement of TRAb levels prior to stopping ATD therapy does aid in predicting which patients can be weaned from the medication, with normal levels indicating a greater chance of remission.<sup>9</sup>
- A patient is in remission if he/she has had a normal serum TSH, free T4, and free T3 for a year after discontinuation of anti-thyroid drugs therapy.
- Relapse is most likely to occur within the first 6-12 months after stopping anti thyroid drugs but may occur years later. Patients with severe hyperthyroidism, large goiters, or persistent high titer of TRAb are most likely to relapse when treatment stops.

All patients should be followed closely for a relapse during the first year after treatment and at least annually thereafter.

6.6.1 Consider stopping carbimazole at the end of 12-18 months treatment, in those patients with Graves' disease, who are likely to undergo remission when drugs are stopped.

6.6.2 For those patients in whom carbimazole cannot be stopped at 18 months, it can be continued for another 12 months or opt for radioactive iodine therapy or total thyroidectomy. <sup>9</sup>

6.6.3 If a patient relapses after remission, definitive treatment with Radioactive iodine therapy or total thyroidectomy is recommended.

6.6.4 Continued long-term anti thyroid drugs can be considered in patients not in remission who prefer this approach. <sup>9</sup>

6.6.5 Once anti-thyroid drugs are stopped, thyroid functions should be checked within 8 weeks of stopping the drug, then every 3 months for a year, then every 6 months for the second year and annually thereafter. <sup>9,11</sup>

## 6.7 Radioactive iodine

- Radioactive iodine is not suitable before puberty or if the patient is trying to become pregnant in the next 6 months.  
Radioactive iodine therapy is usually well tolerated. Complications are rare, except for those related to thyroid eye disease. Radioactive iodine can induce a short-term increase in thyroid hormone levels and thyroid storm may occur very rarely.
- Most patients respond to radioactive iodine therapy with a normalization of thyroid function tests and improvement of clinical symptoms within 4-8 weeks. TSH levels may not normalize for several months after Radioactive Iodine therapy.
- Radioactive iodine treatment is not available locally at present and if required as a treatment option, the patient must be referred to a center abroad where radioactive iodine therapy is offered. Such patients should be referred to and evaluated by an endocrinologist for the need for radioactive iodine therapy and referral abroad.
- For several days following radioactive iodine treatment, patients must adhere to radiation safety precautions to prevent unnecessary radiation exposure to others. This includes avoiding close contact with children and pregnant women.<sup>7</sup>

6.7.1 The decision to offer radioactive iodine therapy and referral abroad for treatment should be taken only after evaluation by an endocrinologist.

- 6.7.2 Pregnancy and breast feeding constitute absolute contraindications to radioactive iodine therapy.
- 6.7.3 Radioactive iodine therapy is not recommended in the presence of moderate to severe active thyroid eye disease.<sup>7,9</sup>
- 6.7.4 If radioactive iodine is the option used for treatment of hyperthyroidism in mild and active thyroid eye disease, steroid prophylaxis is indicated.<sup>13</sup> Prednisolone 0.4-0.5mg/kg/day should be started 1-3 days after radioiodine treatment, continued for 1 month and tapered over 2 months.<sup>14,15</sup>
- 6.7.5 Use of anti-thyroid drugs, before and after Radioactive Iodine therapy is recommended in patients with severe hyperthyroidism, elderly, and individuals with substantial comorbidity that puts them at greater risk for complications and worsening of thyrotoxicosis.
- 6.7.6 Anti-thyroid drugs should be stopped 3-7 days prior to radioactive Iodine administration and resumed after 3-7 days to prevent transient hyperthyroidism and tapered as thyroid function normalizes.
- 6.7.7 Following radioactive iodine therapy, conception should be postponed for at least 6 months for both males and females.<sup>7,9</sup>
- 6.7.8 Measure thyroid function tests at 4-6-weekly intervals for 6 months until TSH becomes normal or until the patient becomes hypothyroid and is stable on thyroid hormone replacement.
- 6.7.9 If TSH remains in the reference range at the end of 6 months, then monitor at 3 monthly intervals till end of 12 months. Further monitoring can be done at 6 monthly intervals or earlier if clinically indicated.
- 6.7.10 If hyperthyroidism persists after 6 months following radioactive iodine therapy, re-treatment with radioactive iodine is recommended.
- 6.7.11 In patients with hyperthyroidism refractory to repeated treatment with radioactive iodine, total thyroidectomy should be recommended.

## 6.8 Thyroidectomy

- Total thyroidectomy aims to remove all overactive thyroid tissue and if surgery is planned, total thyroidectomy is the procedure of choice, because it bears the same risk of complications as subtotal thyroidectomy, while the rate of recurrent hyperthyroidism is lower.<sup>9</sup>

- The advantage of total thyroidectomy is that it immediately cures hyperthyroidism by removing the source of excess thyroid hormone. However, thyroidectomy is a high-cost procedure requiring hospitalization and involves risk related to anesthesia and surgery. Subsequent hypothyroidism necessitates lifelong levothyroxine treatment. <sup>9,11</sup>
- Total thyroidectomy is generally the preferred option in the following settings:
  - moderate-to-severe Graves' eye disease
  - women who desire a pregnancy within the next 6-12 months
  - large goiters causing compressive symptoms or with significant retrosternal extension
  - where thyroid malignancy is suspected
  - when radioactive iodine is contraindicated
- Complications may occur during thyroidectomy, the commonest being transient hypocalcemia and recurrent laryngeal nerve injury but both permanent hypoparathyroidism with hypocalcemia and permanent recurrent laryngeal nerve injury can occur too.  
Post-operative infection, hemorrhage and keloid development are rare. Damage to the superior laryngeal nerve's external branch may occur after thyroidectomy and can have subtle effects on voice projection.

6.8.1 Patients planned for thyroidectomy should be referred to the endocrinologist prior to surgery for evaluation and optimization.

6.8.2 To minimize the risk of complications, thyroid surgery should be performed by a skilled, high-volume surgeon. <sup>7,9,11</sup>

6.8.3 Preoperative ultrasound should be done in all patients with nodules or suspected thyroid cancer.

6.8.4 CT or MRI should be used as an adjunct to ultrasound in selected patients with obstructive features and clinical suspicion of advanced thyroid cancer. Contrast should be given with caution in patients with thyrotoxicosis.

6.8.5 Prior to surgery, the patient must be biochemically euthyroid to reduce the risks of anesthesia and thyroid storm and anti-thyroid drugs should be continued until the day of surgery. <sup>7,9,11</sup>

6.8.6 Patients who do not achieve an euthyroid state with anti-thyroid drugs alone, should be referred to an endocrinologist for treatment with oral iodine (Lugol's solution or saturated potassium iodine solution), beta-blocker and hydrocortisone.

6.8.7 Laryngeal examination with voice assessment should be done prior to performing total thyroidectomy.

- 6.8.8 Vitamin D and calcium levels should be assessed, and patients should be calcium and vitamin D replete prior to surgery to reduce the risk of post-operative transient hypocalcemia and if in doubt can be treated with cholecalciferol for 3 days prior to surgery.<sup>9</sup>
- 6.8.9 After total thyroidectomy, beta blockers should be weaned off and levothyroxine treatment should be started in a weight-appropriate dose.
- 6.8.10 TSH and free T4 should be measured 4-6 weeks after thyroidectomy, and once stable, then at 6 months and then yearly or earlier if clinically indicated.<sup>11</sup>

## 7.0 THYROID STORM

- Patients with hyperthyroidism can present with life-threatening thyrotoxicosis or 'thyroid storm' requiring rapid diagnosis and emergency treatment. The associated clinical picture includes tachycardia, arrhythmia, heart failure, hyperthermia, extreme anxiety, gastrointestinal upset and altered mental state.<sup>9</sup> Thyroid storm may arise in untreated or non-complaint patients or be precipitated by additional factors such as infections, surgery in a patient with unrecognized or inadequately treated hyperthyroidism or occasionally following radioactive iodine therapy.
  - Multiorgan and acute heart failure are the main causes of mortality. Early recognition and treatment in intensive care units with multidisciplinary expertise including endocrinologists, intensivists, cardiologists, and neurologists are required with multiorgan decompensation in patients with thyroid storm.
  - The diagnosis of thyroid storm is made clinically and may be challenging, as often there may be an overlap with clinical features of other critical medical conditions in the patient.
  - The Burch-Wartofsky Score is an objective sensitive tool that aids in diagnosing thyroid storm. It quantitatively scores patients based on clinical features and the presence of a precipitating event (Table 6). A score of  $\geq 45$  is highly suggestive of thyroid storm, a score of 25-44 is suggestive of impending thyroid storm and a score  $< 25$  is unlikely to represent thyroid storm.
- 7.1 Thyroid storm should be managed in an intensive care setting under the care of the endocrinologist with a multidisciplinary approach.
- 7.2 Supportive treatment with airway maintenance, oxygen if needed and intravenous fluids should be provided.

## CLINICAL TREATMENT GUIDELINE FOR THE MANAGEMENT OF HYPERTHYROIDISM IN ADULTS

- 7.3 High doses of Propylthiouracil (500-1000 mg loading, then 250 mg, 4-6 hourly) should be used in thyroid storm. In the presence of contraindications to propylthiouracil, high doses of carbimazole (60-80 mg/day) can be used.
- 7.4 B-blockers such as propranolol (blocks peripheral conversion of T4 to T3 in high doses), intravenous esmolol or metoprolol should be administered to control heart rate and inhibit other peripheral action of thyroid hormones.
- 7.5 Diltiazem can be used to control heart rate if beta blocker is contraindicated.
- 7.6 Lugol's iodine (5-10 drops) should be administered 6-8 hourly for the first 10 days and should be given after 30-60 minutes of administration of antithyroid drugs for rapid improvement of thyrotoxicosis in thyroid storm.
- 7.7 High doses of glucocorticoids (IV hydrocortisone 100 mg, 6 hourly or dexamethasone 2 mg, 6 hourly) should be given in thyroid storm.
- 7.8 All patients with thyroid storm should have early definitive therapy with radioactive iodine or total thyroidectomy.
- 7.9 In patients with large obstructing goiter or contraindications to radioactive iodine therapy, early total thyroidectomy should be considered.

<b>Table 6: Burch-Wartofsky Score: Diagnostic Criteria for Thyroid storm</b>			
<b>Criteria</b>	<b>Score</b>	<b>Criteria</b>	<b>Score</b>
<b>Thermoregulatory dysfunction</b>		<b>Cardiovascular dysfunction</b>	
<b>Temperature (F)</b>		<b>Tachycardia (bpm)</b>	
99-99.9	5	90- 109	5
100-100.9	10	110-119	10
101-101.9	15	120-129	15
102-102.9	20	130 -139	20
103-103.9	25	≥140	25
≥104	30		
<b>CNS effects</b>		<b>Congestive heart failure</b>	
<b>Absent</b>	<b>0</b>	<b>Absent</b>	<b>0</b>
<b>Mild</b>	<b>10</b>	<b>Mild</b>	<b>5</b>
Agitation		Pedal edema	
<b>Moderate</b>	<b>20</b>	<b>Moderate</b>	<b>10</b>
Delirium		Bibasilar rales	
Psychosis		<b>Severe</b>	<b>15</b>
Extreme lethargy		Pulmonary edema	
<b>Severe</b>	<b>30</b>		
Seizure			
Coma			
<b>GI - hepatic Dysfunction</b>		<b>Atrial fibrillation</b>	
<b>Absent</b>	<b>0</b>	<b>Absent</b>	<b>0</b>
<b>Moderate</b>	<b>10</b>	<b>Present</b>	<b>10</b>
Diarrhea		<b>Precipitant history</b>	
Nausea/vomiting			
Abdominal pain			
<b>Severe</b>	<b>20</b>	<b>Negative</b>	<b>0</b>
Unexplained jaundice		<b>Positive</b>	<b>10</b>
<p>A score of ≥45 is highly suggestive of thyroid storm, a score of =25-44 is suggestive of impending thyroid storm and a score &lt;25= is unlikely to represent thyroid storm</p>			

## 8.0 MANAGEMENT OF THYROID EYE DISEASE (THYROID ORBITOPATHY)

- Thyroid associated orbitopathy occurs mostly in those with Graves’ disease and includes inflammation of the eyes, eye muscles and surrounding tissues.
- The most common signs of thyroid eye disease are eyelid retraction, lid lag of the upper eyelid on downward gaze and lid edema. Thyroid eye disease is the most common cause of proptosis in adults. Other clinical features include lagophthalmos, exposure keratopathy, chemosis, conjunctival injection, restrictive extraocular motility, and compressive optic neuropathy.  
Compressive optic neuropathy, often heralded by dyschromatopsia, decreased vision, and/or visual field defects, is considered an ophthalmic emergency requiring immediate treatment
- Patients typically have symptoms of ocular surface discomfort, such as tearing, dry eyes, swelling of the lids, or redness of the lids or conjunctiva.
- Assessment of thyroid eye disease includes assessment of disease activity and severity using standardized criteria as treatment decisions are based on the severity and activity of the disease.  
Early diagnosis of eye involvement and measures to prevent progression should be practiced. Smoking is the most important known risk factor for the worsening of thyroid eye disease and patients should be advised to stop smoking.

### 8.1 Assessment of Severity of Thyroid eye disease

- **The European Group of Graves Orbitopathy System is widely used for broad categorization of thyroid eye disease severity.** The tool grades the severity of thyroid eye disease into 3 categories mild, moderate to severe, and sight threatening thyroid eye disease and is a useful tool for directing therapy. (Table7)

Grade	Lid retraction	Soft tissues	proptosis	diplopia	Corneal exposure
mild	< 2mm	Mild involvement	< 3mm	Transient or absent	Absent
Moderate to severe	≥ 2mm	Moderate or Severe involvement	≥ 3 mm	Inconstant or constant	Mild
Sight threatening	-	-	-	-	Dysthyroid Optic neuropathy and/ or corneal breakdown and/or globe subluxation 17

## 8.2 Assessment of Activity of Thyroid eye disease

- The active phase of orbitopathy is best described by the Clinical Activity Score (CAS), which is the most widely used tool to assess thyroid eye disease activity.<sup>15</sup>
- CAS is generated by the addition of one point for each of the following features if present (Table 8).
- Thyroid orbitopathy is considered active in patients with a CAS  $\geq 3$ .<sup>15</sup>

Feature	points
Painful feeling behind the globe over the last 4 weeks	1 point
Pain with eye movement during the last 4 weeks	1 point
Chemosis	1 point
Eyelid swelling	1 point
Eyelid erythema	1 point
Conjunctival redness	1 point
Caruncula swelling	1 point
Decreased visual acuity >1 line on Snellen chart compared with previous visit	1 point
Increased proptosis > 2mm compared with previous visit	1 point
Decreased eye movement >5° any direction compared with previous visit	1 point
The Clinical Activity Score ranges from 0 to 10 points. A 7-point scale, lacking the last three elements, is used when no previous assessment is available	

## 8.3 Treatment of Thyroid eye disease

### 8.3.1 General measures

- 8.3.1.1 Advise and offer counselling for patients to quit smoking and refer them to a smoking cessation clinic if available.<sup>15</sup>
- 8.3.1.2 The evaluation and management of thyroid eye disease should be managed by a multi-disciplinary team including endocrinologists and ophthalmologists.
- 8.3.1.3 Assessment of thyroid eye disease should include assessment of both disease Activity and Severity.
- 8.3.1.4 Urgent referral to the ophthalmologist should be done in the presence of sight threatening eye disease.

8.3.1.5 Treatment with local artificial tears during the day and ophthalmic gels/ointments with a possible taping of the lids or using swimming goggles / eye masks at nighttime should be advised, to prevent or treat corneal exposure.<sup>15,17</sup>

### 8.3.2 Inactive orbitopathy

8.3.2.1 The treatment option for hyperthyroidism can be selected independent of orbitopathy.<sup>9,13</sup>

8.3.2.2 Elective rehabilitative surgery of the eye such as strabismus or eyelid surgery should be offered to patients after the thyroid eye disease has been inactive for at least 6 months and when it is associated with significant impact on visual function or quality of life.

### 8.3.3 Mild thyroid eye disease

8.3.3.1 A single course of supplementation of selenium (100 mcg twice daily) for 6 months may be given as it is likely to improve and prevent progression of thyroid eye disease.<sup>15,17</sup>

8.3.3.2 In mild and active orbitopathy the treatment option for hyperthyroidism can be selected independent of orbitopathy.<sup>9,13</sup>

### 8.3.4 Moderate and severe thyroid eye disease

8.3.4.1 Rapid correction of hyperthyroidism with anti-thyroid drugs.

8.3.4.2 Treatment of hyperthyroidism with Radioactive iodine is contraindicated in moderate (active), severe or sight threatening eye disease.

8.3.4.3 Intravenous steroid i.e. 4.5g methylprednisolone (IVMP) given in 12 weekly infusions (0.5g weekly X 6 weeks followed by 0.25g weekly for an additional 6 weeks) is indicated.

8.3.4.4 The cumulative dose of intravenous methylprednisolone should not be more than 8g.<sup>15,17</sup>

- Glucocorticoid infusions should be started after ruling out any underlying infection. Cardiovascular risk, liver enzymes and markers of viral hepatitis are to be evaluated before treatment to assess risks and contraindications. Recent viral hepatitis, significant hepatic dysfunction, severe cardiovascular morbidity, or psychiatric disorders, represent contraindications to glucocorticoid infusions, while diabetes and hypertension should be well controlled before starting treatment.<sup>15</sup>

- 8.3.4.5 In the case of use of oral glucocorticoids, treatment should be with prednisolone 60mg-100mg daily, gradually tapered down by 5-10 mg/ week until withdrawal in 3 months. <sup>17</sup>
- 8.3.4.6 Poor response to IV Methyl prednisolone at 6 weeks should prompt consideration for treatment withdrawal and evaluation of other second line- therapies.
- 8.3.4.7 Clinicians should be alert for worsening diplopia or disease progression even while on IV methyl prednisolone therapy.
- 8.3.4.8 Local subconjunctival/periocular injections of triamcinolone acetate may be considered when systemic glucocorticoids are absolutely contraindicated. <sup>15</sup>
- 8.3.4.9 Radiotherapy is an option in patients whose principal feature is progressive diplopia but should be used with caution in diabetes to avoid possible retinopathy
- 8.3.4.10 Surgery for moderate to severe eye disease should be performed by a surgeon experienced in these procedures and complications.

### **8.3.5 Sight-threatening thyroid eye disease**

- 8.3.5.1 It is an emergency because of the risk of sight loss due to dysthyroid optic neuropathy and/or corneal breakdown.
- 8.3.5.2 It should be managed by a multi-disciplinary team including ophthalmologists and endocrinologists.
- 8.3.5.3 Hyperthyroidism must be treated with anti-thyroid drugs
- 8.3.5.4 Immediate treatment with high-dose intravenous methylprednisolone (0.5-1g of methylprednisolone daily for either 3 consecutive days or on alternate days) while monitoring daily.
- 8.3.5.5 If there is no or inadequate response or deterioration of ophthalmic signs after 2 weeks of treatment, urgent orbital decompression surgery should be undertaken. <sup>15,17</sup>

## 9.0 HYPERTHYROIDISM AND PREGNANCY

- Poorly controlled thyrotoxicosis is associated with adverse maternal and fetal outcomes. Due to changes in maternal thyroid physiology during pregnancy, assessment and interpretation of thyroid function tests may be challenging.
- Significant but reversible changes in maternal thyroid physiology take place from the very first weeks of gestation. High concentrations of circulating estrogens result in increased thyroxine binding globulin concentrations, which is responsible for an increase in total T4 and T3 levels, accompanied by a decrease in free thyroid hormone levels.  
During the first trimester, the thyroid gland is stimulated by increased levels of human chorionic gonadotrophin(hCG), that acts as a thyrotropic agonist leading to transient increase in free thyroid hormone levels and reduced serum TSH levels. From mid-gestation, as hCG declines, serum fT4 and fT3 concentrations decline gradually, while serum TSH concentrations rise slightly.
- Because of the above changes, TSH levels during pregnancy are shifted downwards compared to non-pregnant population, especially during early gestation. Detection of TSH levels below or near the lower limit of the reference range during the 1st trimester of pregnancy may not be indicative of maternal hyperthyroidism, as they are found in as many as 15% healthy women at this stage of pregnancy. Nonetheless, if a suppressed serum TSH is found, further biochemical investigations and accurate clinical evaluation should be performed to exclude/confirm hyperthyroidism

### 9.1 Preconception counselling

- Women of reproductive age, with hyperthyroidism should receive preconception counselling to minimize maternal and fetal adverse outcomes as both hyperthyroidism and its treatment may result in complications. Patients should be informed that fetal prognosis may be affected by the transplacental passage of maternal thyroid stimulating antibodies (TRAb) or anti thyroid drugs, both of which may disrupt fetal thyroid function. Maternal liver injury and birth defects have been reported in association with the use of antithyroid drugs and rarely, may cause fetal/neonatal hyperthyroidism.
- 9.1.1 Pre-conception counselling should be done for all women of childbearing age who are thyrotoxic and should review the risk and benefits of all treatment options and the patients desired timeline to conception.
- 9.1.2 Patients should be informed about the increased risk of associated birth defects with antithyroid drugs

- 9.1.3 Thyrotoxic women should be ideally rendered euthyroid before pregnancy.
- 9.1.4 Women trying to conceive and choosing to continue anti thyroid drugs should be switched to propylthiouracil at the lowest effective dose to maintain free T4 concentrations in the upper half of the reference range .<sup>9</sup>
- 9.1.5 The option of definitive treatment with radioactive iodine or total thyroidectomy should be considered in women with severe hyperthyroidism Following radioactive iodine therapy, women should wait at least 6 months before trying to conceive. <sup>12</sup>.

## 9.2 Evaluation of thyroid function tests in pregnancy

- 9.2.1 All pregnant women should be screened for thyroid dysfunction at first contact with a healthcare professional.
- 9.2.2 TSH value should be evaluated in conjunction with either TT4 and TT3, with TT4 and TT3 reference value adjusted at 1.5 times the non-pregnant range or fT4 trimester specific normal reference ranges (if available).
- 9.2.3 When a suppressed TSH is detected in the first trimester (less than the reference range), medical history, physical examination and measurement of maternal serum fT4 or TT4 concentrations should be performed. Measurement of TRAb and maternal TT3 may prove helpful in clarifying the etiology of thyrotoxicosis.
- 9.2.4 Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy.
- 9.2.5 Overt hyperthyroidism is confirmed in the presence of suppressed serum TSH and inappropriately elevated TT4/fT4 or TT3.
- 9.2.6 TRAb should be done in the first trimester in all patients with history of Graves' disease in the past treated with radioactive iodine or thyroidectomy, even following definitive treatment.
- 9.2.7 If TRAb levels are low or undetectable in early pregnancy, no further TRAb testing is recommended.
- 9.2.8 If patient is being treated with anti-thyroid drugs or initial TRAb level elevated, TRAb should be measured again between 18 to 22 weeks.

- 9.2.9 If patient is on anti-thyroid drugs in the third trimester or if TRAb level elevated at 18-22 weeks, a TRAb measurement should again be done at 30 to 34 weeks to evaluate the risk of fetal and neonatal hyperthyroidism.

### 9.3 Treatment of Hyperthyroidism in pregnancy

- 9.3.1 Hyperthyroidism during pregnancy should be managed by a multi-disciplinary approach with close collaboration between endocrinologists, obstetricians, pediatricians and neonatologists
- 9.3.2 Propylthiouracil is recommended as first line agent in women planning pregnancy and during the first trimester of pregnancy.
- 9.3.3 If a woman gets pregnant while on carbimazole, a switch to Propylthiouracil should be made if before 10-12 weeks of gestation.<sup>12</sup>
- 9.3.4 Cessation of anti-thyroid drugs, if possible, is recommended early in gestation (6-10 weeks), before the major teratogenic period. Following cessation of anti-thyroid drugs, thyroid function tests and clinical examination should be performed every 1 to 2 weeks.  
The decision to stop medication should consider the disease history, goiter size, duration of therapy, results of recent thyroid function tests, TRAb level and other clinical factors.
- 9.3.5 For women who are euthyroid for 6 months or more on a low dose of antithyroid drugs (carbimazole <10 mg/day or PTU <200 mg/day), anti-thyroid drugs may be stopped during gestation with close monitoring of thyroid function tests.
- 9.3.6 The lowest effective dose should be used for thyrotoxicosis during pregnancy, targeting T4 concentrations in the upper half of the reference range.
- 9.3.7 Long-term treatment with beta blockers should be avoided in pregnancy, since they may cause intrauterine growth restriction, fetal bradycardia, and neonatal hypoglycemia.
- 9.3.8 TSH and fT4/T4 should be measured every 2-4 weeks after the initiation of therapy.
- 9.3.9 Thyroid function tests should be done 6 to 8 weeks after delivery.
- 9.3.10 Anti thyroid drugs can be continued during breast feeding and the lowest effective dose should be given during the lactation period.

## 9.4 Gestational transient thyrotoxicosis

- Gestational transient thyrotoxicosis results from the transient increase in thyroid hormones that occur with elevated human chorionic gonadotropin (hCG) levels in pregnant women, without evidence of thyroid autoimmunity and resolves spontaneously by the end of the 1st or early 2nd trimester of pregnancy. It is often associated with hyperemesis gravidarum in early pregnancy, which manifests as severe nausea and vomiting, resulting in dehydration and weight loss.

**Table 9: Features distinguishing Gestational Transient Thyrotoxicosis from Graves' Disease**

Feature	Gestational Transient Thyrotoxicosis (GTT)	Graves' Disease
Symptoms of thyrotoxicosis BEFORE pregnancy	No	Yes
Symptoms of Hyperemesis Gravidarum (nausea/vomiting)	Yes, often present	Often not present
Prior history of thyroid disease	No	Often present
Signs of thyroid eye disease	No	May be present
Presence of goitre	No	Yes, often present
TRAb measurement	Normal	Increased

- In early pregnancy, the differential diagnosis in majority of cases is between Graves' hyperthyroidism and gestational transient thyrotoxicosis (Table 9). Findings with no prior history of thyroid disease, no stigmata of Graves' Disease (goiter, orbitopathy), self-limited mild disorder and symptoms of emesis favour the diagnosis of gestational transient thyrotoxicosis.
- Consider doing TRAb level, as new onset Graves' disease in pregnancy is likely to be associated with raised TRAb levels and doing it can avoid the unnecessary starting of anti-thyroid drugs in gestational transient thyrotoxicosis.<sup>12</sup>

9.4.1 Manage gestational transient thyrotoxicosis through supportive therapy with anti-emetics, rehydration and hospitalization if needed, in the presence of hyperemesis gravidarum.

9.4.2 B-blocker can be considered, if very symptomatic.

9.4.3 Anti-thyroid drugs are not indicated in gestational transient thyrotoxicosis.

## 9.5 Fetal monitoring

- Uncontrolled hyperthyroidism and elevated TRAb levels adversely affect fetal health with increased risk for fetal hyperthyroidism and these patients need to be closely monitored for proper fetal management. The diagnosis of fetal hyperthyroidism is made on clinical grounds based on maternal history, serum TRAb levels and fetal ultrasonography to detect intrauterine thyroid dysfunction.
- Ultrasonographic signs suggestive of fetal hyperthyroidism include presence of fetal goiter, sustained fetal heart rate >160-170 bpm, accelerated bone maturation, intra uterine growth restriction, oligo/polyhydramnios, congestive cardiac failure and fetal hydrops.
  - 9.5.1 Fetal monitoring should be performed in women with uncontrolled hyperthyroidism in the second half of gestation and/or with high TRAb levels (more than 3 three times upper limit of normal) detected at any time during pregnancy.
  - 9.5.2 Patients should be managed with a multidisciplinary team approach including endocrinologists, experienced obstetricians, pediatricians, neonatologist and maternal-fetal medicine specialist if available
  - 9.5.3 TRAb should be remeasured between 18 to 22 weeks and 30 to 34 weeks to evaluate the risk of fetal and neonatal hyperthyroidism.
  - 9.5.4 Ultrasonographic surveillance of the fetus should be done, with initial fetal ultrasound performed at 18-22 weeks and then at every 4 weeks to assess for gestational age, fetal viability, amniotic fluid volume, fetal anatomy, and detection of malformations
  - 9.5.5 Neonates of women with known Graves' disease, of those taking anti thyroid drugs during pregnancy and with increased TRAb levels should have their thyroid function tests done soon after birth and then at 1-2 weeks after. <sup>12</sup>

## 9.6 Postpartum thyroiditis

- Postpartum thyroiditis is an autoimmune condition causing thyroid dysfunction, within the first 12 months following a pregnancy in a previously euthyroid woman. Post partum thyroiditis classically begins with an initial transient hyperthyroid phase followed by a transient hypothyroid phase and then a return to euthyroid state.
- The thyrotoxic phase of post-partum thyroiditis typically occurs between 2 and 6 months postpartum and resolves spontaneously. This thyrotoxic phase needs to be distinguished from Graves' Disease in the postpartum period (Table 10).

- Investigations show raised thyroid hormones (fT4>fT3), low TSH and low radioiodine uptake. A high TRAb titer would support relapse of GH. If the diagnosis remains unclear, radioiodine uptake can help distinguish between GH and PPT in a non-breast-feeding woman.

**Table 10: Features differentiating the thyrotoxic phase of postpartum thyroiditis from Grave’s disease**

	Postpartum thyroiditis (thyrotoxic phase)	Graves’ disease (new/relapse)
Timing of onset	Within 3 months of delivery	After 6 months of delivery
Severity of clinical features	Mild	Usually, severe
Goiter	Small	Usually, larger May have bruit
Ophthalmopathy	Absent	May be present
FT3 and FT4	Mild elevation FT4 > FT3 Usually, normalizes in 3-4 weeks	Higher levels FT3 > FT4 Persistently abnormal
TRAb	Negative	May be positive
Thyroid USG with Doppler flow	Low flow	High flow
<sup>99</sup> mTc scan*	Low uptake	High uptake

\* Use of <sup>99</sup>mTc scan requires avoiding breast feeding on the day of the scan

- 9.6.1 Usually self-limiting and anti-thyroid drugs are not indicated in the thyrotoxic phase of post-partum thyroiditis.
- 9.6.2 Women in thyrotoxic phase who are symptomatic should be treated with lowest possible dose of b-blockers such as propranolol (40-120mg daily in three divided doses), 20-50mg daily atenolol and metoprolol which are safe in breast feeding.
- 9.6.3 Resolution of thyrotoxic phase should be followed by monitoring thyroid function tests in 4-8 weeks, to screen for the hypothyroid phase.
- 9.6.4 Women in hypothyroid phase who are symptomatic or actively trying to become pregnant or breast feeding, should be treated with levothyroxine.
- 9.6.5 For women in hypothyroid phase who have been started on levothyroxine therapy, discontinuation of levothyroxine should be attempted after 12 months post-partum, tapering should be gradual and TSH monitored every 6-8 weeks.

- 9.6.6 Women in hypothyroid phase who are not initiated on levothyroxine, can be managed expectantly with thyroid function monitoring every 4-8 weeks until an euthyroid state is restored.
- 9.6.7 In women with resolution of post-partum thyroiditis and restoration of euthyroid state, serum TSH should be monitored annually as they continue to be at risk of developing permanent hypothyroidism.

## 9.7 Breastfeeding and anti-thyroid drugs

- 9.7.1 Anti thyroid drugs are considered safe during breastfeeding and the lowest effective dose of antithyroid should be administered during the period of lactation with monitoring of the child's growth and development.
- 9.7.2 Consideration may be given to administering the total daily dose of anti-thyroid drugs in two or three smaller doses a day after the mother has breast fed.

## 10.0 HYPERTHYROIDISM AND SURGERY

- Surgical stress and anesthesia can precipitate thyroid storm, cardiac failure or tachyarrhythmias in patients with uncontrolled pre-existing hyperthyroidism.

### 10.1 Elective surgery

- 10.1.1 In patients with subclinical hyperthyroidism, surgery can proceed as planned and generally does not require pre-operative treatment. In patients with high risk such as the elderly and/or patients with cardiovascular disease, the use of preoperative beta blockers is sufficient to minimize the risk of arrhythmia.<sup>13</sup>
- 10.1.2 In patients with overt hyperthyroidism, elective surgeries should be postponed pending adequate control of thyroid hormones (normal free T4 and free T3). Anti thyroid drugs should be given and continued post operatively.
- 10.1.3 Beta blockers should be given peri-operatively, starting a week before surgery if time allows and should be continued throughout the post-operative period.<sup>13</sup>
- 10.1.4 In patients undergoing thyroidectomy, antithyroid drugs should be stopped after surgery.

## 10.2 Emergency surgery

- 10.2.1 In subclinical hyperthyroidism, the use of preoperative beta blockers in patients with high risk such as the elderly and younger patients with cardiovascular disease is sufficient.
- 10.2.2 In patients with overt hyperthyroidism, anti-thyroid drugs should be initiated as soon as possible as surgery cannot be postponed.
- 10.2.3 A thorough evaluation for cardiac and pulmonary diseases, and any development of arrhythmia, cardiac ischemia, and heart failure should be done.
- 10.2.4 Cardiac status must be optimized with the use of perioperative beta blockers and closely monitored.
- 10.2.5 When there is an urgent need to stabilize the thyroid hormones rapidly, iodide (Lugol's iodine) should be given as an adjunct to anti thyroid drugs, after 30 minutes of administration of antithyroid drugs.
- 10.2.6 Glucocorticoids (hydrocortisone 100mg IV 8 hourly, or dexamethasone 2 mg IV 6 hourly) may be added preoperatively and tapered over 3 days as it decreases the conversion of thyroxine to triiodo thyronine.<sup>13</sup>

## 11.0 SUBCLINICAL HYPERTHYROIDISM

- Subclinical hyperthyroidism is defined as suppressed serum TSH with normal free T4 and free T3 concentrations in 2 readings done 3 months apart. When clinically indicated, where TSH <0.1 or risk factors are present, thyroid function tests could be done earlier, within few weeks of the initial test.
- Subclinical hyperthyroidism is associated with osteoporosis, fractures, atrial fibrillation, heart failure and increased risk of mortality from cardiovascular events especially in those with serum TSH level <0.1mIU/L.<sup>9</sup>
- Treatment should be considered in patients with subclinical hyperthyroidism who are either elderly (age >65 years old) OR with comorbidities (cardiac disease or osteoporosis) or TSH level <0.1mIU/L.
- Patients with subclinical hyperthyroidism at a younger age (age<65 years) and those without comorbidities (cardiac disease or osteoporosis) AND TSH between 0.1 and 0.5 mIU/L and asymptomatic should be observed (Table 9).<sup>7,9</sup>

**Table 9: Factors influencing consideration of treatment of subclinical hyperthyroidism**

Factor	TSH <0.1mIU/L	TSH (0.1-0.4 mIU/L)
Age > 65 years	Yes <sup>9</sup>	Consider treating <sup>9</sup>
Age<65 years with comorbidities	Yes <sup>9</sup>	Consider treating <sup>9</sup>
Heart disease	Yes	Consider treating
osteoporosis	Yes	Consider treating
Menopausal (not on estrogen or bisphosphonate)	Yes	Consider treating
Hyperthyroid symptoms	Yes	Consider treating
Age<65 years, asymptomatic	Consider treating	Observe

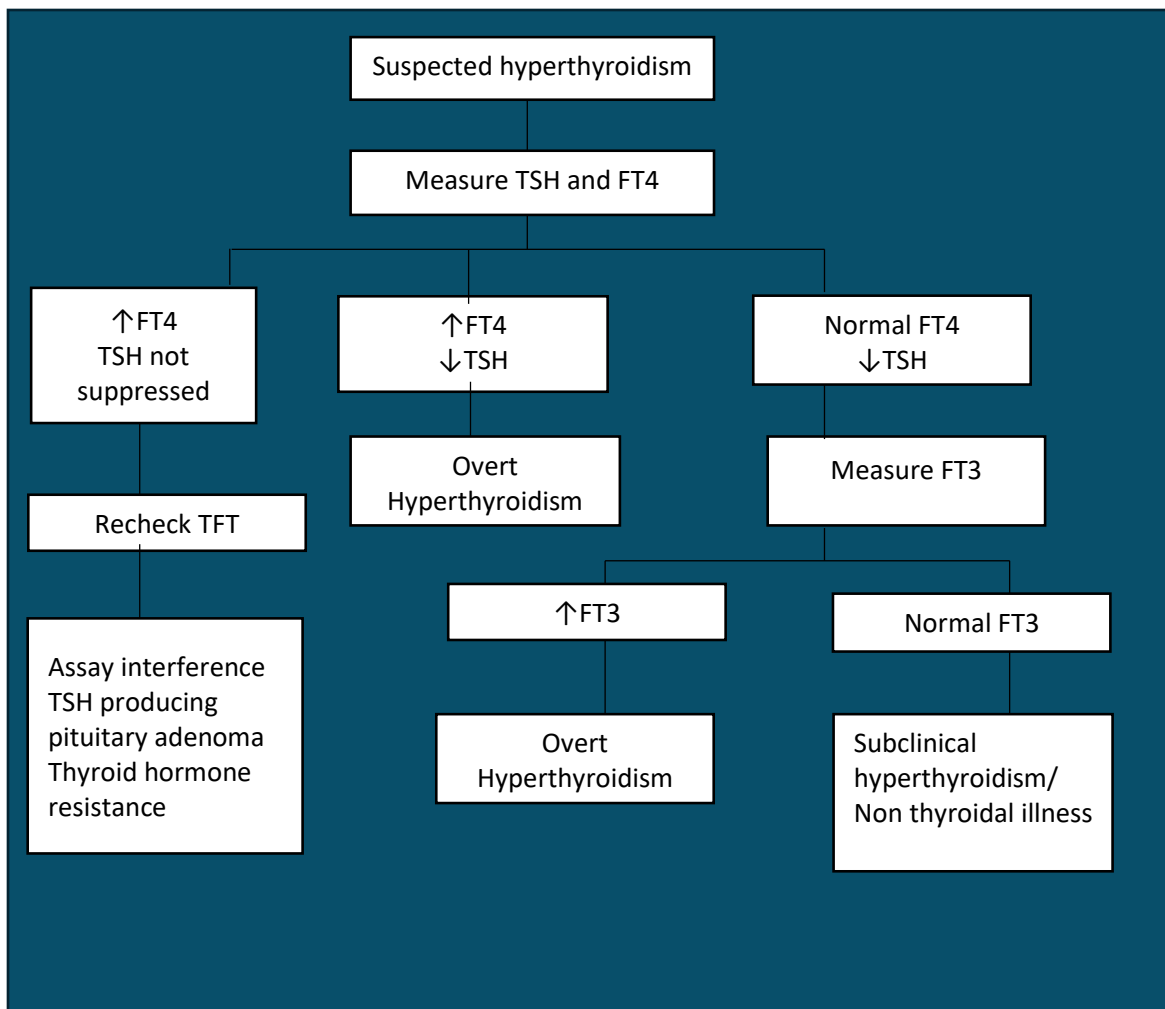
- 11.1 Anti-thyroid drugs should be the first line of treatment for subclinical hyperthyroidism, whatever the etiology.
- 11.2 Radioactive iodine therapy should be considered in those with persistent and progressive subclinical hyperthyroidism due to an autonomous nodule and multinodular goiter.
- 11.3 Surgery should be reserved for those with compressive symptoms (dysphagia and shortness of breath) or suspicious of malignancy.
- 11.4 For adults with untreated subclinical hyperthyroidism measure TSH every 6 months. If the TSH level is outside the reference range, then measure fT4 and fT3.<sup>11</sup>
- 11.5 Consider stopping TSH measurement if the TSH level has remained within the reference range on 2 measurements 3 to 6 months apart.<sup>11</sup>

## 12.0 REFERRAL OF PATIENTS TO ENDOCRINOLOGY

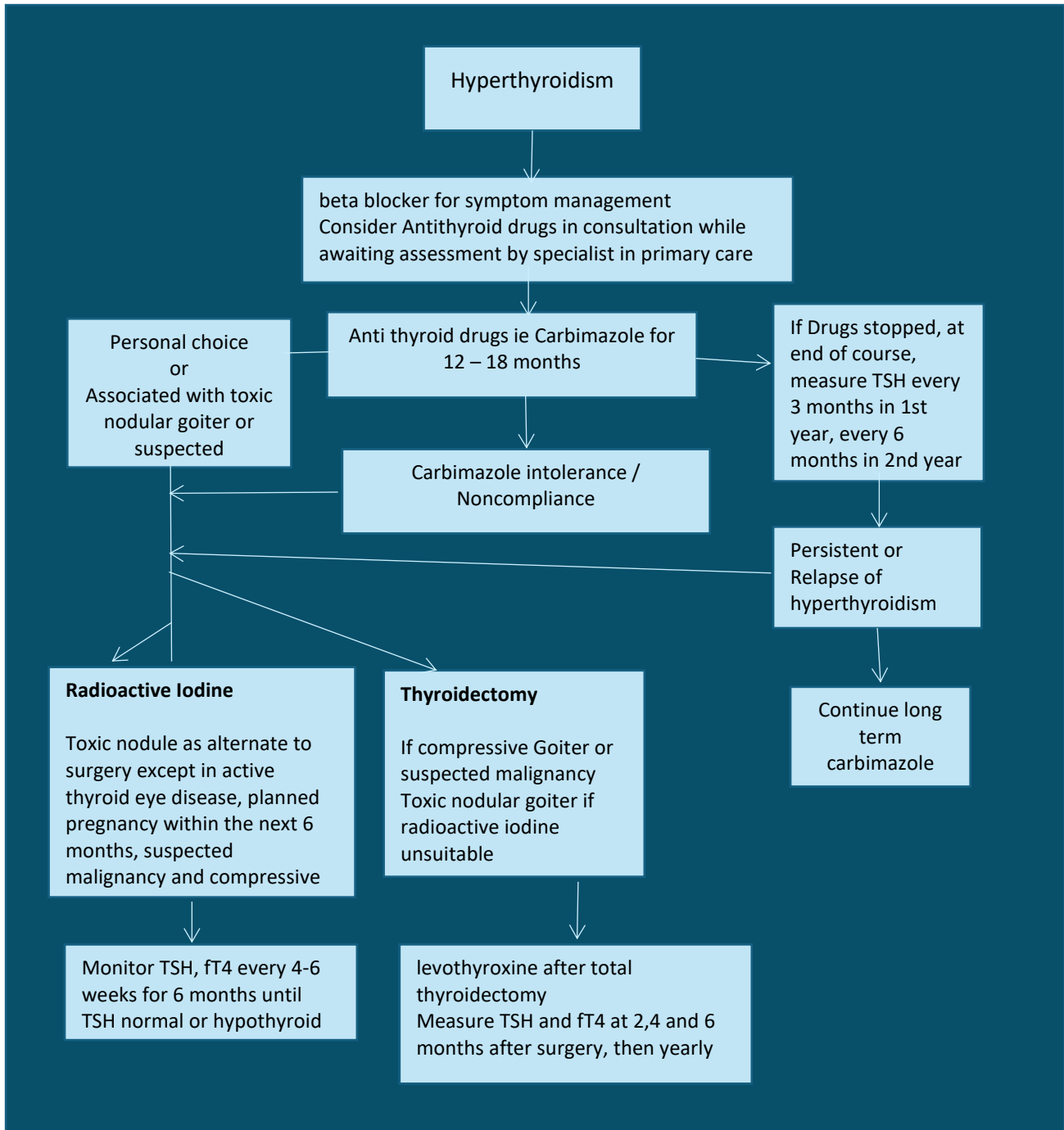
- Hyperthyroidism being treated with anti-thyroid drugs but remaining hyperthyroid despite adequate treatment, relapsed after initial course of treatment
- Hyperthyroidism in pregnancy
- Hyperthyroidism due to Toxic multinodular goiter or Toxic adenoma
- Hyperthyroid patients with other comorbidities or who develop comorbidities
- Thyroid eye disease, co management with ophthalmologists

## 13.0 CLINICAL PATHWAYS

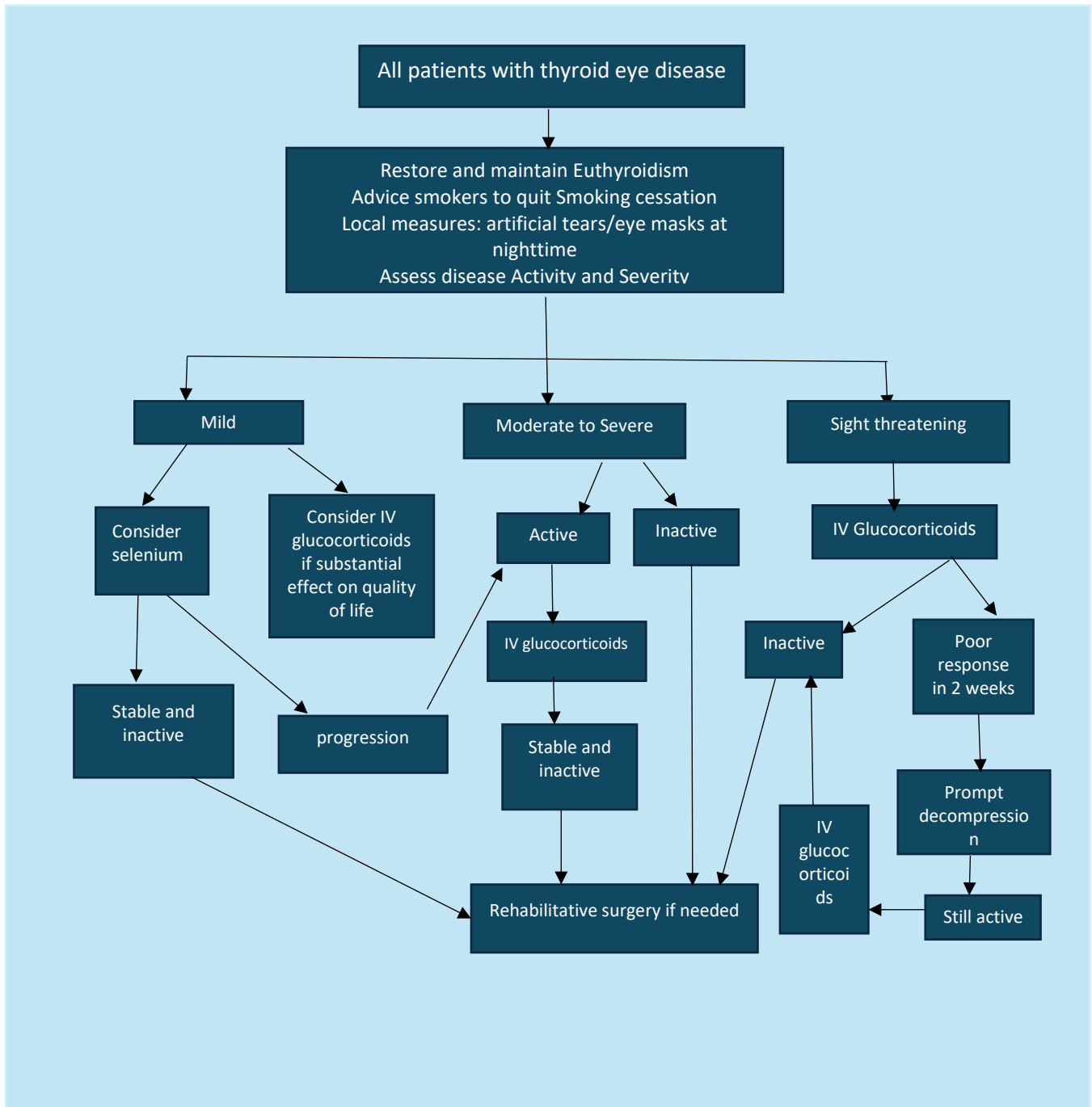
### 13.1 Algorithm for investigation of suspected hyperthyroidism



### 13.2 Algorithm for Management of hyperthyroidism



### 13.3 Algorithm for the management of thyroid eye disease



## 14. REFERENCES

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